## REMARKS

Applicants' attorney thanks the Examiner for the courtesy of a telephone interview on June 3, 2004. Participating in the interview were the Examiner, applicants' attorney Barry F. McGurl, as well as Adriane Antler and Douglas Bradley. The rejections under 35 U.S.C. §§ 101 and 103 were discussed. In response to the remarks made regarding the rejections, the Examiner stated that the § 101 rejection would not be withdrawn, but agreed to reconsider the § 103 rejection.

The foregoing amendments serve to clarify the claimed subject matter. In particular, Claims 38, 56 and 70 have been amended to clarify that each unit in the plurality of units confines the specified probe. Applicants note that the "plurality" of units need not be all the units in the probe matrix; all that is required is that such a plurality be present. Support for the claim amendments is found in the specification at least at page 4, lines 20-22, and at page 5, lines 17-19. In view of the foregoing claim amendments and arguments that follow, reconsideration and favorable action are requested.

### Oath/Declaration

Enclosed herewith is a properly executed Power of Attorney for the instant application.

### Rejection of Claim 69 Under 35 U.S.C. § 101

The Examiner rejects Claim 69 because the claimed invention is allegedly directed to data in computer-readable memory which is allegedly not patentable subject matter. Applicants respectfully submit that the Examiner has mischaracterized the subject matter encompassed by Claim 69. Claim 69 is directed to a computer memory (*i.e.*, a computer-readable medium) storing an output signal data structure database produced by the method of Claim 56.



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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

It is well established that functional descriptive material recorded on a computer-readable memory is patentable "When functional descriptive material is recorded on some computer-readable medium (e.g. a computer memory) it becomes structurally and functionally interrelated to the medium and will be statutory in most cases since use of technology permits the function of the descriptive material to be realized." M.P.E.P. § 2106(IV)(B)(1), citing *In re Lowry*, 32 U.S.P.Q.2d 1031, 1035 (Fed. Cir. 1994).

A definition of functional descriptive material is provided in M.P.E.P. § 2106(IV)(B)(1):

> "Functional descriptive material consists of data structures and computer programs which impart functionality when employed as a computer component. (The definition of 'data structure' is 'a physical or logical relationship among data elements, designed to support specific data manipulation functions.' citation omitted)"

The material stored in the computer memory encompassed by Claim 69 includes a data structure database wherein stored digital signals are associated (I) with a stimulus and (II) with the identity of an identified gene. This stored information imparts the function of permitting a user to associate a stimulus with the identity of an identified gene, and to use that information and association to gain insights into the function of biological cells and organisms. Thus, the information stored in the computer memory is functional descriptive material recorded on a computer-readable memory, and so is patentable subject matter.

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Also, M.P.E.P. § 2106(IV)(B)(1)(a) (at p. 2100-13, col. 2) states:

> "When a computer program is recited in conjunction with a physical structure, such as a computer memory, Office personnel should treat the claim as a product claim."

For the foregoing reasons, applicants respectfully request that the examiner withdraw the rejection of Claim 69 under 35 U.S.C. § 101.

Rejection of Claims 38-53, 55-66, 68-83, and 85 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Gress et al. in View of Granelli-Piperno et al, in View of Fodor et al.

Applicants reiterate the arguments, made in response to the same rejection in parent Patent Application Number 09/294,453, set forth in the preliminary amendment filed on October 31, 2002. For the sake of brevity applicants have not repeated all of these arguments in this response, but refer the Examiner to the aforementioned preliminary amendment. Additionally, the Examiner is asked to consider the arguments that follow.

The Examiner's Proposed Modification Renders the Gress et al. Method Unsatisfactory for its Intended Purpose: It is well established that if a proposed modification would render a prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *See, In re Gordon*, 733 F2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

The Gress et al. publication (*Mammalian Genome 3*:609-619 (1992)) discloses a method for characterizing large numbers of cDNA library clones, and is useful, for example, to identify cDNA clones that are abundantly expressed in several tissues, and that are likely to encode proteins involved in structural and regulatory functions in every cell. The identified cDNA

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

clones can then be partially sequenced, so as to allow the correlation of genomic mapping, transcriptional and sequence information into a global data set (see Gress et al. at p. 609, col. 1, last 2 sentences, and col. 2, 1st paragraph, last sentence; p. 610, col. 1, 2nd paragraph, last sentence). In the practice of the Gress et al. method, thousands of unidentified cDNA clones from human fetal brain, and from *Drosophila* embryos, are arrayed on a nitrocellulose filter, and hybridized against a labeled cDNA pool derived from mouse tissues. Partial sequence data for clones of interest are then generated (see Gress et al. at sentence spanning p. 617 to p. 618) (Only a small number of *Drosophila* cDNA clones were sequenced in Gress et al. in order to demonstrate the applicability of the approach to the *Drosophila* genome; see Gress et al. at p. 613, col. 2, 1st paragraph.)

The Examiner argues that it would have been obvious to modify the method of Gress et al. by using an array of probes which each have a pre-determined sequence as disclosed by Fodor et al., because Fodor et al. shows that such an array has the advantage of allowing the sequences detected in the sample to be mapped to a particular location of the genome of the organism sampled.

Applicants submit that the Examiner's proposal to replace the thousands of unidentified cDNA clones that are arrayed on a nitrocellulose filter, or other substrate, as taught by Gress et al., with oligonucleotides having known sequences, would render the Gress et al. invention inoperable for its intended purpose. For example, in the Gress et al. publication thousands of unidentified cDNA clones from human fetal brain, and from *Drosophila* embryos, are arrayed on a nitrocellulose filter, and hybridized against a labeled cDNA pool derived from mouse tissues. The strongly hybridizing clones are selected for sequencing because these are likely to encode highly expressed proteins that are involved in structural and regulatory functions in every cell, and which are conserved throughout a wide range of species. The successful



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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

practice of the Gress et al. method does not require any knowledge of the identity or sequence of the cDNA clones that are being sought. Indeed, it would be nonsensical to use probes of known sequence in order to determine which of the probes of known sequence will be sequenced.

Moreover, modification of the Gress et al. invention to replace the thousands of unidentified cDNA clones arrayed on a substrate with thousands of probes which each have a pre-determined sequence, as suggested by the Examiner, would only permit an investigator to identify the expression pattern of those clones in the pool that happen to hybridize to one of the pre-determined sequences. Clones that do not hybridize to one of the pre-determined sequences could not be screened using the modified method of Gress et al. Even if the pre-determined sequences were selected to hybridize to thousands of different expressed genes (or cDNAs derived therefrom), one of ordinary skill in the art would have to know at least part of the sequence of each of the thousands of different expressed genes (or cDNAs derived therefrom).

Consequently, applicants submit that it is not obvious to modify the Gress et al. method by incorporating the teachings of the Fodor et al. publication as suggested by the Examiner. Moreover, the Granelli-Piperno et al. publication, cited by the Examiner, does not cure the deficiencies of Gress et al., since it does not teach a plurality of units, ordered in a probe matrix, each of which confines a probe comprising a pre-determined nucleotide sequence.

Moreover, particularly regarding Claims 49, 50 and 51, as well as Claims 63, 64 and 65, and Claims 80, 81 and 82, Granelli-Piperno, alone or in combination with the other references, does not render obvious these claims because Granelli-Piperno only teaches studying the effect of the stimulus on the expression of a small subset of genes in a cell. Granelli-Piperno is interested in analyzing the control of lymphokine mRNA levels (see page 922, third full paragraph), and thus looks at the levels of mRNAs of nine different genes in stimulated T cells (see paragraph spanning pages 924-925). In contrast, each of the aforementioned set of claims

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

specify that the probe matrix comprises probes having sequences that are hybridizable with at least 0.5%, 5% or 50%, respectively, of the genes of the living thing (or with transcripts of at least 0.5%, 5% or 50%, respectively, of the genes, or with the cDNA derived from at least 0.5%, 5% or 50%, respectively of the genes). Thus, these claims are nonobvious for this additional reason.

Consequently, applicants submit that Claims 38-53, 55-56, 68-83, and 85 are not obvious in view of Gress et al. in view of Granelli-Piperno et al. in view of Fodor et al.

Rejection of Claims 38, 48-51, 54, 56, 63-65, 67, 70, 80-82, and 84 Under 35 U.S.C. § 103(a) as Being Allegedly Unpatentable Over Gress et al. in View of Granelli Piperno et al. in View of Fodor et al. and Further in View of Watson et al.

The Examiner characterizes the rejected Claims as being drawn to assays utilizing fungal cells, and cites Watson et al., pp. 573-575, for its teaching that these cells contain genes that are regulated by stimuli such as metabolites.

For the reasons set forth in the preceding section, applicants submit that it is not obvious to combine the teachings of Gress et al. and Fodor et al. as suggested by the Examiner. This deficiency is not cured by the teachings of either Granelli-Piperno et al. or Watson et al..

Moreover, applicants submit that Granelli-Piperno et al. teaches away from the present invention. Applicants submit that Granelli-Piperno et al. is not concerned with the problem addressed and solved by the present invention.

Granelli-Piperno et al only teaches studying the effect of specific stimuli on the expression of a small subset of genes in T cells. Granelli-Piperno is interested in analyzing the control of lymphokine mRNA levels (see page 922, third full paragraph), and thus looks at the levels of mRNAs of nine different genes in stimulated T cells (see paragraph spanning pages 924-925). Little or no information will be obtained other than that which is specifically sought.

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

In contrast, the present invention is discovery oriented. The present invention provides methods that can be used to provide information on the cellular response stimulated by any agent that affects cells regardless of the cellular target of the agent and associated changes in gene expression. For example, one need not have any information or hypothesis regarding the cellular targets (*e.g.*, receptor molecules) or genes that respond to the agent in order to practice the present invention. This is in direct contrast to Granelli-Piperno et al, where a small number of genes are analyzed that are expressed in T cells, and whose expression provides information about a well-characterized T cell response (the production of lymphokines).

Consequently, applicants submit that Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-21 and 84 are not obvious in view of the combination of Gress et al. in view of Granelli-Piperno et al. in view of Fodor et al. and further in view of Watson et al.

The Cited Art Does Not Teach or Suggest All of the Claim Limitations: Applicants respectfully point out an additional reason that the rejected claims are nonobvious over the cited combination of references. Even, assuming *arguendo*, that Gress et al., Fodor et al., and Granelli-Piperno et al., optionally in combination with Watson et al., could be properly combined, the combination still does not teach step (c) of Claim 38, 56 or 70, i.e., storing a digital signal associated with (i) the stimulus, and (ii) the identity of the identified gene (to which the pre-determined sequence of the probe is hybridizable). Gress et al.'s teachings are discussed above; there is no hint or suggestion in Gress et al. of storing a digital signal in association with a stimulus and the identity of the identified gene. In addition to not disclosing an array, Granelli-Piperno et al. does not disclose the transduction of physical signals into electrical output signals, much less storing the signal in digital form associated with a stimulus and the identity of the identified gene. Applicants further note that, contrary to the Examiner's contention, Table I of Granelli-Piperno et al. does not show levels of IL-2 and IFN-γ mRNA; instead, Table I, under

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

the columns IL-2 and IFN-γ, shows protein activity levels measured by bioassay, and protein levels measured by radioimmunoassay, which is clearly distinct from the electrical output signal generated by the nucleic acid hybridization step (a) of the claims. Fodor et al. does not disclose characterizing the effects of a stimulus, much less storing a digital signal associated with a stimulus and the identity of the identified gene. Watson et al. does not cure the foregoing deficiencies. Thus, for this additional reason, the rejected claims are nonobvious.

Double Patenting: The Examiner rejects certain claims under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 5,777,888 in view of Fodor et al.

Submitted herewith is a terminal disclaimer with respect to Patent No. 5,777,888.

## CONCLUSIONS

In view of the foregoing arguments and amendments, applicants respectfully submit that all of the pending claims are in condition for allowance. Reconsideration and favorable action are requested.

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS[PLLC]

Barry F. McGurl
Registration No. 43,340
Direct Dial No. 206.695.1775

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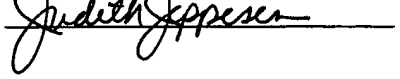
Date: 7/12/04 

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LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100